MESNEX - mesna tablet
Baxter Healthcare Corporation

DESCRIPTION

MESNEX is a detoxifying agent to inhibit the hemorrhagic cystitis induced by ifosfamide (IFEX). The active ingredient mesna is a synthetic sulfhydryl compound designated as sodium-2-mercaptoethane sulfonate with a molecular formula of $C_2H_5NaO_3S_2$ and a molecular weight of 164.18. Its structural formula is as follows:

$HS—CH_2—CH_2SO_3—Na^+$

MESNEX Injection is a sterile, nonpyrogenic, aqueous solution of clear and colorless appearance in clear glass multidose vials for intravenous administration. MESNEX Injection contains 100 mg/mL mesna, 0.25 mg/mL edetate disodium and sodium hydroxide for pH adjustment. MESNEX Injection multidose vials also contain 10.4 mg of benzyl alcohol as a preservative. The solution has a pH range of 7.5-8.5.

MESNEX Tablets are white, oblong, scored biconvex film-coated tablets with the imprint M4. They contain 400 mg mesna. Excipients include lactose, microcrystalline cellulose, calcium phosphate, cornstarch, povidone, magnesium stearate, hydroxypropylmethylcellulose, polyethylene glycol, titanium dioxide, and simethicone.

CLINICAL PHARMACOLOGY

Mechanism of Action

MESNEX was developed as a prophylactic agent to reduce the risk of hemorrhagic cystitis induced by ifosfamide.

Analogous to the physiological cysteine-cystine system, mesna is rapidly oxidized to its major metabolite, mesna disulfide (dimesna). Mesna disulfide remains in the intravascular compartment and is rapidly eliminated by the kidneys.

In the kidney, the mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites (acrolein and 4-hydroxy-ifosfamide) resulting in their detoxification. The first step in the detoxification process is the binding of mesna to 4-hydroxy-ifosfamide forming a nonurotoxic 4-sulfoethylthioifosfamide. Mesna also binds to the double bonds of acrolein and to other urotoxic metabolites.

In multiple human xenograft or rodent tumor model studies of limited scope, using IV or IP routes of administration, mesna in combination with ifosfamide (at dose ratios of up to 20-fold as single or multiple courses) failed to demonstrate interference with antitumor efficacy.

Pharmacokinetics

At doses of 2-4 g/m^2, the terminal elimination half-life of ifosfamide is about 4-8 hours. As a result, in order to maintain adequate levels of mesna in the urinary bladder during the course of elimination of the urotoxic ifosfamide metabolites, repeated doses of MESNEX are required.

IV-IV-IV Regimen

After intravenous administration of an 800-mg dose, the half-lives of mesna and dimesna in the blood are 0.36 hours and 1.17 hours, respectively. Approximately 32% and 33% of the administered dose was eliminated in the urine in 24 hours as mesna and dimesna, respectively. The majority of the dose recovered was eliminated within 4 hours. Mesna has a plasma clearance of 1.23 L/h/kg.

IV-Oral-Oral Regimen

The half-life of mesna ranged from 1.2-8.3 hours after administration of intravenous plus oral doses of MESNEX, as recommended in the DOSAGE AND ADMINISTRATION section. The urinary bioavailability of oral mesna ranged from 45-79% of intravenously administered mesna. Food does not affect the urinary availability of orally administered mesna. Approximately 18-26% of the combined intravenous and oral mesna dose appears as free mesna in the urine. When compared to intravenously administered mesna, the intravenous plus oral dosing regimen increases systemic exposures (150%) and provides more sustained excretion of mesna in the urine over a 24-hour period. Approximately 5% of the mesna dose is excreted during the 12-24 hour interval, as compared to negligible amounts in patients given the IV regimen. The fraction of the administered dose of mesna excreted in the urine is independent of dose. Protein binding of mesna is in a moderate range (69-75%).

Special Populations

Gender Effect

An analysis was conducted in four male and four female volunteers; no differences in plasma pharmacokinetics were detected.

Pediatrics and Geriatrics

Pharmacokinetic data of MESNEX in pediatric and geriatric patients are not available.

Hepatic and Renal Insufficiency
No clinical studies were conducted to evaluate the effect of hepatic impairment or renal impairment on the pharmacokinetics of MESNEX.

Drug-Drug Interaction
No clinical drug interaction studies have been conducted with MESNEX.

Clinical Studies

IV Mesna

Hemorrhagic cystitis produced by ifosfamide is dose dependent (Table 1). At a dose of 1.2 g/m^2 ifosfamide administered daily for 5 days, 16-26% of the patients who received conventional uroprophylaxis (high fluid intake, alkalinization of the urine, and the administration of diuretics) developed hematuria (>50 RBC/hpf or macrohematuria) (Morgan, Einhorna, Costanzi). In contrast, none of the patients who received MESNEX Injection together with this dose of ifosfamide developed hematuria (Einhorna,b). In two randomized studies, (Fukuoka, Scheef), higher doses of ifosfamide, from 2 to 4 g/m^2 administered for 3-5 days, produced hematuria in 31-100% of the patients. When MESNEX was administered together with these doses of ifosfamide, the incidence of hematuria was less than 7%.

Table 1

Percent of MESNEX Patients Developing Hematuria (≥50 RBC/hpf or macrohematuria)

Study	**Conventional Uroprophylaxis (number of patients)**	**Standard MESNEX IV Regimen (number of patients)**
Uncontrolled Studies		
MORGAN*	16% (7/44)	-
COSTANZI*	26% (11/43)	-
EINHORN[a]*	18% (7/38)	0% (0/21)
EINHORN[b]*	-	0% (0/32)
Controlled Studies		
FUKUOKA†	31% (14/46)	6% (3/46)
SCHEEF†	100% (7/7)	0% (0/8)

*Ifosfamide dose 1.2 g/m^2 d x 5

†Ifosfamide dose 2 to 4 g/m^2 d x 3-5

Oral Mesna
Clinical studies comparing recommended intravenous and oral mesna dosing regimens demonstrated incidences of grade 3-4 hematuria of <5%. Study D07093-0018 was an open label, randomized, two-way crossover study comparing three IV doses with an initial IV dose followed by two oral doses of mesna in patients with cancer treated with ifosfamide at a dose of 1.2-2.0 g/m^2 for 3-5 days. Study MED504 was a randomized, multicenter study in cancer patients receiving ifosfamide at 2.0 g/m^2 for 5 days. In both studies, development of grade 3 or 4 hematuria was the primary efficacy endpoint. The percent of patients developing hematuria in each of these studies is presented in Table 2.

Table 2

Percent of MESNEX Patients Developing Grade 3 or 4 Hematuria

	MESNEX Dosing Regimen	
Study	**Standard IV Regimen (number of patients)**	**IV + Oral Regimen (number of patients)**
D07093-0018	0% (0/30)	3.6% (1/28)
MED504	3.7% (1/27)	4.3% (1/23)

A crossover pharmacokinetic study supports the low incidence of grade 3 or 4 hematuria with the recommended intravenous and oral mesna dosing regimens used in the two controlled studies.

INDICATIONS AND USAGE
MESNEX is indicated as a prophylactic agent in reducing the incidence of ifosfamide-induced hemorrhagic cystitis.

CONTRAINDICATIONS
MESNEX is contraindicated in patients known to be hypersensitive to mesna or other thiol compounds.

WARNINGS
Allergic reactions to mesna ranging from mild hypersensitivity to systemic anaphylactic reactions have been reported. Patients with autoimmune disorders who were treated with cyclophosphamide and mesna appeared to have a higher incidence of allergic reactions. The majority of these patients received mesna orally.
MESNEX has been developed as an agent to reduce the risk of ifosfamide-induced hemorrhagic cystitis. It will not prevent or alleviate any of the other adverse reactions or toxicities associated with ifosfamide therapy.
MESNEX does not prevent hemorrhagic cystitis in all patients. Up to 6% of patients treated with mesna have developed hematuria (>50 RBC/hpf or WHO grade 2 and above). As a result, a morning specimen of urine should be examined for the presence of hematuria (microscopic evidence of red blood cells) each day prior to ifosfamide therapy. If hematuria develops when MESNEX is given with ifosfamide according to the recommended dosage schedule, depending on the severity of the hematuria, dosage reductions or discontinuation of ifosfamide therapy may be initiated.
In order to reduce the risk of hematuria, MESNEX must be administered with each dose of ifosfamide as outlined in the DOSAGE AND ADMINISTRATION section. MESNEX is not effective in reducing the risk of hematuria due to other pathological conditions such as thrombocytopenia.
Because of the benzyl alcohol content, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

PRECAUTIONS

Information for Patients
Healthcare providers should advise patients taking MESNEX to drink at least a quart of liquid a day. Patients should be informed to report if their urine has turned a pink or red color, if they vomit within 2 hours of taking oral MESNEX, or if they miss a dose of oral MESNEX. See Patient Information Leaflet for MESNEX Tablets.

Laboratory Tests
A false positive test for urinary ketones may arise in patients treated with MESNEX. In this test, a red-violet color develops which, with the addition of glacial acetic acid, will return to violet.

Drug Interactions
No clinical drug studies have been conducted.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
No long-term studies in animals have been performed to evaluate the carcinogenic potential of MESNEX.

Mutagenesis
Mesna was not genotoxic in the *in vitro* Ames bacterial mutagenicity assay, the *in vitro* mammalian lymphocyte chromosomal aberration assay or the *in vivo* mouse micronucleus assay.

Impairment of Fertility
No studies on male or female fertility were conducted. No signs of male or female reproductive organ toxicity were seen in 6-month oral rat studies (at doses up to 2000 mg/kg/day) or 29-week oral dog studies (520 mg/kg/day; both studies approximately 10-fold higher than the maximum recommended human dose on a body surface area basis).

Pregnancy

Pregnancy Category B
Reproduction studies have been performed in rats and rabbits at oral doses of 1000 mg/kg in rabbits and 2000 mg/kg in rats (approximately 10 times the maximum recommended total daily IV-oral-oral human dose on a body surface area basis) and have revealed no evidence of harm to the fetus due to mesna. There are however, no adequate and well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether mesna or dimesna is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from mesna, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Safety and effectiveness of MESNEX Tablets in pediatric patients have not been established.
Because of the benzyl alcohol content in MESNEX Injection, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients.

Geriatric Use
Clinical studies of mesna did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. However, the ratio of ifosfamide to mesna should remain unchanged.

ADVERSE REACTIONS
MESNEX adverse reaction data are available from four phase I studies in which single IV bolus doses of 600-1200 mg MESNEX Injection without concurrent chemotherapy were administered to a total of 53 subjects and single oral doses of 600-2400 mg of MESNEX Tablets were administered to a total of 82 subjects.
The most frequently reported side effects (observed in two or more patients) for patients receiving single doses of MESNEX IV were headache, injection site reactions, flushing, dizziness, nausea, vomiting, somnolence, diarrhea, anorexia, fever, pharyngitis, hyperaesthesia, influenza-like symptoms, and coughing. Among patients who received a single 1200-mg dose as an oral solution, rigors, back pain, rash, conjunctivitis, and arthralgia were also reported. In two phase I multiple-dose studies where patients received MESNEX Tablets alone or IV MESNEX followed by repeated doses of MESNEX Tablets, flatulence and rhinitis were reported. In addition, constipation was reported by patients who had received repeated doses of IV MESNEX.
Because mesna is used in combination with ifosfamide or ifosfamide-containing chemotherapy regimens, it is difficult to distinguish the adverse reactions which may be due to MESNEX from those caused by the concomitantly administered cytotoxic agents.
Adverse reactions reasonably associated with mesna administered IV and orally in four controlled studies in which patients received ifosfamide or ifosfamide-containing regimens are presented in Table 3.

Table 3

Incidence of Adverse Events and Incidence of Most Frequently Reported Adverse Events in Controlled Studies

Mesna Regimen	IV-IV-IV	IV-Oral-Oral
N exposed	119 (100.0%)	119 (100.0%)
Incidence of AEs	101 (84.9%)	106 (89.1%)
Most Frequently Reported Adverse Events (Preferred Terms)		
	N (%)	N (%)
Nausea	65 (54.6)	64 (53.8)
Vomiting	35 (29.4)	45 (37.8)
Constipation	28 (23.5)	21 (17.6)
Leukopenia	25 (21.0)	21 (17.6)
Fatigue	24 (20.2)	24 (20.2)
Fever	24 (20.2)	18 (15.1)
Anorexia	21 (17.6)	19 (16.0)
Thrombocytopenia	21 (17.6)	16 (13.4)
Anemia	20 (16.8)	21 (17.6)
Granulocytopenia	16 (13.4)	15 (12.6)
Asthenia	15 (12.6)	21 (17.6)
Abdominal Pain	14 (11.8)	18 (15.1)
Alopecia	12 (10.1)	13 (10.9)
Dyspnea	11 (9.2)	11 (9.2)
Chest Pain	10 (8.4)	9 (7.6)
Hypokalemia	10 (8.4)	11 (9.2)
Diarrhea	9 (7.6)	17 (14.3)

Dizziness	9 (7.6)	5 (4.2)
Headache	9 (7.6)	13 (10.9)
Pain	9 (7.6)	10 (8.4)
Sweating Increased	9 (7.6)	2 (1.7)
Back Pain	8 (6.7)	6 (5.0)
Hematuria*	8 (6.7)	7 (5.9)
Injection Site Reaction	8 (6.7)	10 (8.4)
Edema	8 (6.7)	9 (7.6)
Edema Peripheral	8 (6.7)	8 (6.7)
Somnolence	8 (6.7)	12 (10.1)
Anxiety	7 (5.9)	4 (3.4)
Confusion	7 (5.9)	6 (5.0)
Face Edema	6 (5.0)	5 (4.2)
Insomnia	6 (5.0)	11 (9.2)
Coughing	5 (4.2)	10 (8.4)
Dyspepsia	4 (3.4)	6 (5.0)
Hypotension	4 (3.4)	6 (5.0)
Pallor	4 (3.4)	6 (5.0)
Dehydration	3 (2.5)	7 (5.9)
Pneumonia	2 (1.7)	8 (6.7)
Tachycardia	1 (0.8)	7 (5.9)
Flushing	1 (0.8)	6 (5.0)

*All grades

Postmarketing Surveillance
Allergic reactions, decreased platelet counts associated with allergic reactions, hypertension, hypotension, increased heart rate, increased liver enzymes, injection site reactions (including pain and erythema), limb pain, malaise, myalgia, ST-segment elevation, tachycardia, and tachypnea have been reported as part of postmarketing surveillance.

OVERDOSAGE
There is no known antidote for MESNEX. Oral doses of 6.1 and 4.3 g/kg were lethal to mice and rats, respectively. These doses are approximately 15 and 22 times the maximum recommended human dose on a body surface area basis. Death was preceded by diarrhea, tremor, convulsions, dyspnea, and cyanosis.

DOSAGE AND ADMINISTRATION
For the prophylaxis of ifosfamide induced hemorrhagic cystitis, MESNEX may be given on a fractionated dosing schedule of three bolus intravenous injections or a single bolus injection followed by two oral administrations of MESNEX Tablets as outlined below.

Intravenous Schedule
MESNEX is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration and 4 and 8 hours after each dose of ifosfamide. The total daily dose of mesna is 60% of the ifosfamide dose.
The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Ifosfamide	1.2 g/m^2	–	–
MESNEX	240 mg/m^2	240 mg/m^2	240 mg/m^2

Intravenous and Oral Dosing
MESNEX Injection is given as intravenous bolus injections in a dosage equal to 20% of the ifosfamide dosage (w/w) at the time of ifosfamide administration. MESNEX Tablets are given orally in a dosage equal to 40% of the ifosfamide dose 2 and 6 hours after each dose of ifosfamide. The total daily dose of mesna is 100% of the ifosfamide dose.
The recommended dosing schedule is outlined below:

	0 Hours	2 Hours	6 Hours
Ifosfamide	1.2 g/m^2	–	–

MESNEX Injection	240 mg/m^2	–	–
MESNEX Tablets	–	480 mg/m^2	480 mg/m^2

Patients who vomit within two hours of taking oral mesna should repeat the dose or receive intravenous mesna. The efficacy and safety of this ratio of IV and PO mesna has not been established as being effective for daily doses of IFEX higher than 2.0 g/m^2. The dosing schedule should be repeated on each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted (either increased or decreased), the ratio of MESNEX to IFEX should be maintained.

Preparation of Intravenous Solutions/Stability
The MESNEXmultidose vials may be stored and used for up to 8 days.
For IV administration the drug can be diluted by adding the MESNEX Injection solution to any of the following fluids obtaining final concentrations of 20 mg mesna/mL:
- 5% Dextrose Injection, USP
- 5% Dextrose and 0.2% Sodium Chloride Injection, USP
- 5% Dextrose and 0.33% Sodium Chloride Injection, USP
- 5% Dextrose and 0.45% Sodium Chloride Injection, USP
- 0.92% Sodium Chloride Injection, USP
- Lactated Ringer's Injection, USP

For example:
One mL of MESNEX Injection multidose vial 100 mg/mL may be added to 4 mL of any of the solutions listed above to create a final concentration of 20 mg mesna/mL.
Diluted solutions are chemically and physically stable for 24 hours at 25°C (77°F).
Mesna is not compatible with cisplatin or carboplatin.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

HOW SUPPLIED
MESNEX (mesna) Injection 100 mg/mL
- NDC 0338-1305-01 1 g Multidose Vial, Box of 1 vial of 10 mL
- NDC 0338-1305-03 1 g Multidose Vial, Box of 10 vials of 10 mL
  Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]

MESNEX (mesna) Tablets
- NDC 67108-3565-9 400 mg scored tablets packaged in box of 10 tablets
  Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]

MESNEX (mesna) Injection manufactured by:
MESNEX (mesna) Tablets manufactured for:
Baxter, Mesnex and Ifex are trademarks of Baxter International Inc.
U.S. Patent Nos.:5,262,169, 5,252,341 and 5,696,172
Baxter Healthcare Corporation
Deerfield, IL 60015 USA
For Product Inquiry 1 800 ANA DRUG (1-800-262-3784)
Made in Germany
Rev Feb 2009
USA C 18
HA-30-01-119

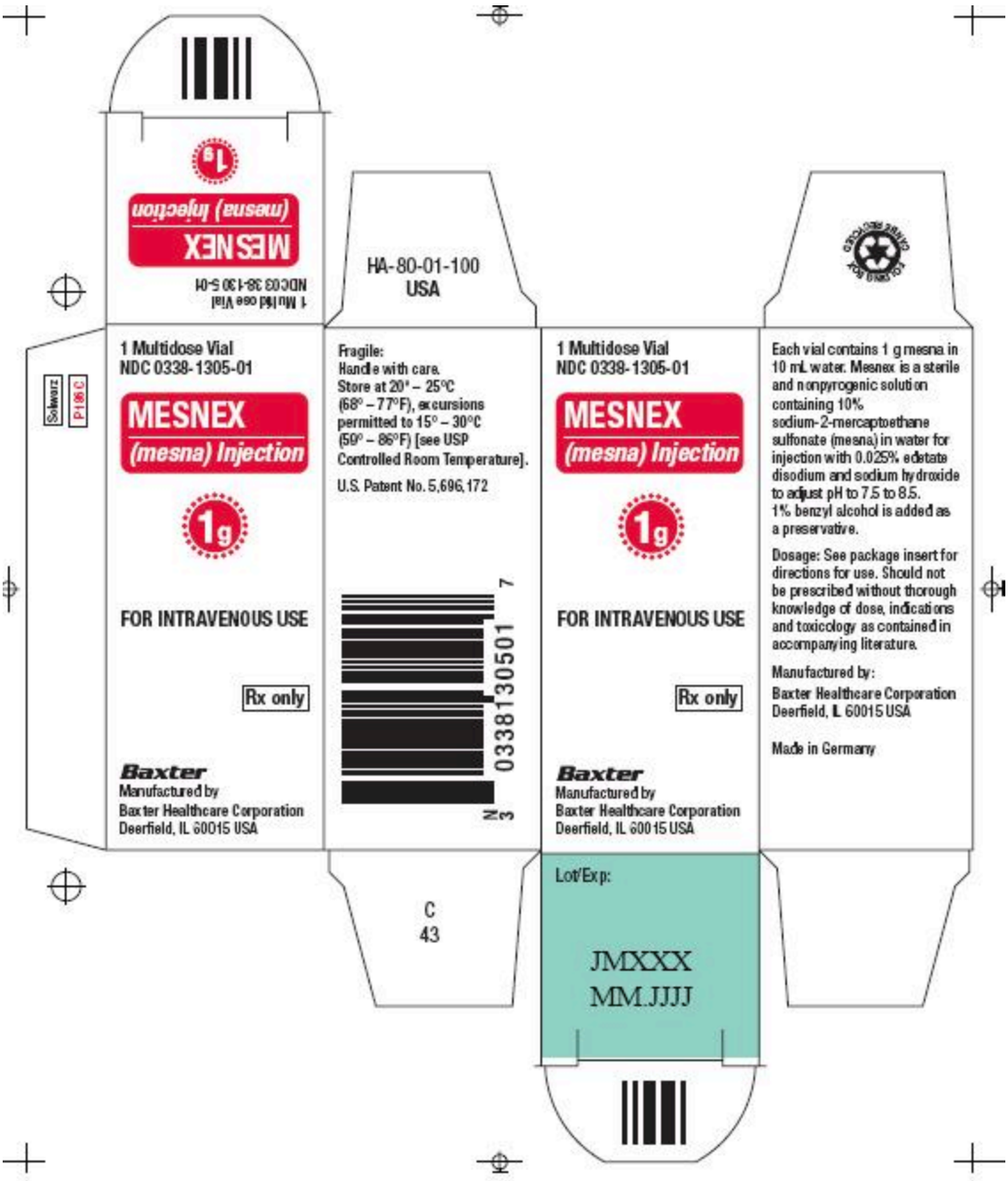
PACKAGE LABEL - PRINCIPAL DISPLAY PANEL

Container Label - Vial

Container Label 1g Multidose Vial

1 Multidose Vial
NDC 0338-1305-01
Mesnex (mesna) Injection
FOR INTRAVENOUS USE
1g
Rx only

Carton Label - Vial



Carton Label 1g Multidose Vial

1 Multidose Vial
NDC 0338-1305-01
Mesnex (mesna) Injection
1g
FOR INTRAVENOUS USE
Rx only
Baxter
Manufactured by
Baxter Healthcare Corporation
Deerfield, IL 60015 USA

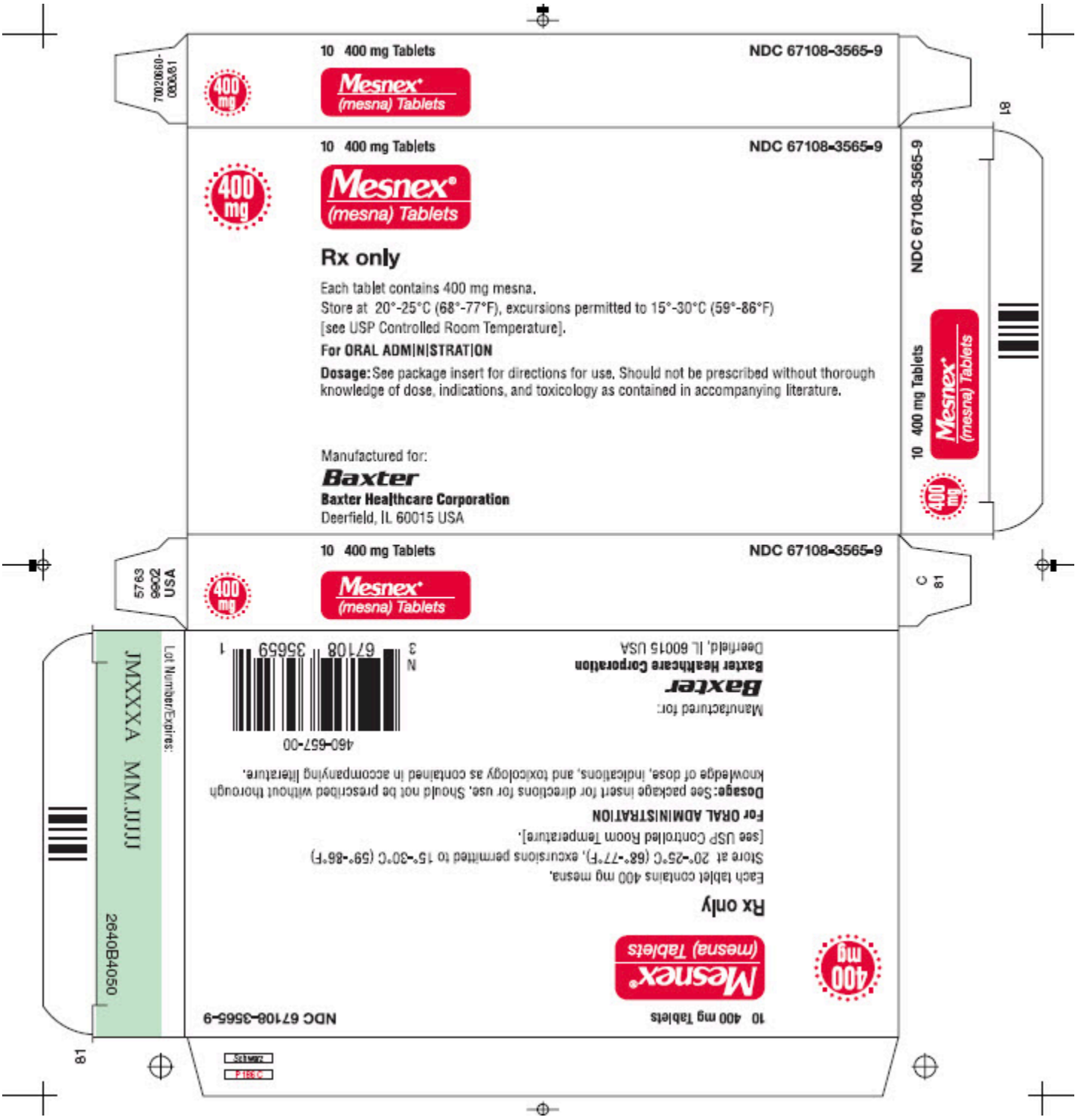
Container Label - Tablets

Container Label 400 mg Tablets

List 3565-9
Rx only
400 mg
Mesnex
(mesna) Tablets
Baxter Healthcare Corporation
460-656-00
USA 5363 9222
(01)00067108356590
Lot-number:/Expires:

JMXXX
MM.JJJJ

Carton Label - Tablets



Carton Label 400 mg Tablets

10 400 mg Tablets
NDC 67108-3565-9
400 mg
Mesnex
(mesna) Tablets
Rx only

Each tablet contains 400 mg mesna.
Store at 20°-25°C (68°-77°F), excursions permitted to 15°-30°C (59°-86°F)
[see USP Controlled Room Temperature].
For ORAL ADMINISTRATION
Dosage: See package insert for directions for use. Should not be prescribed without thorough knowledge of dose, indications, and toxicology as contained in accompanying literature.
Manufactured for:
Baxter
Baxter Healthcare Corporation
Deerfield, IL 60015 USA